

Claims

1. Semicarbazide derivatives of formula I

5 A-D-B (I)

wherein

D is a bivalent semicarbazide moiety, or a derivative thereof,

10 A is a unsubstituted or substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L')_{\alpha}$, where L is a 5, 6 or 7 membered cyclic structure, preferably selected from the group consisting of aryl, heteroaryl, arylene and heteroarylene, bound
15 directly to D, L' comprises an optionally substituted cyclic moiety having at least 5 members, preferably selected from the group consisting of aryl, heteroaryl, aralkyl, cycloalkyl and heterocyclyl, M is a bond or a bridging group having at least to one atom, α is an integer of from 1-4; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen,
20 oxygen and sulfur, wherein L' is preferably substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$

25 B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbo atoms, preferably of up to 20 carbon atoms, comprising at least one 5-, 6-, or 7-membered cyclic structure, preferably a 5- or 6-membered cyclic structure, bound directly to D containing 0-4 members of the group consisting of

30 nitrogen, oxygen and sulfur, wherein said cyclic structure directly bound to D is preferably selected from the group

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5 consisting of aryl, heteroaryl and heterocyclyl, which is optionally substituted by 1-5 substituents, preferably selected from alkyl, halogen, C₁-C₆ haloalkyl, C₃-C₇ cycloalkyl, heterocyclyl, aryl, aralkyl, heteroaryl, alkoxy, haloalkoxy, aralkoxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfenyl, carbamoyl, amino and amino alkylene;

10 R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

15 R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

20 R_x is R_z or NR_aR_b, where R_a and R_b are

25 a) independently hydrogen, a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

30 -OSi(R_f)₃ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based

substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

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or

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- b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

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- c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

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where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_γ , where γ is 0-3;

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wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R$, $-C(O)NR^4R^4$, $-C(O)-R^4$, $-NO_2$, $-OR^4$, $-SR^4$, $-NR^4R^4$, $-NR^4C(O)OR^4$, $-NR^4C(O)R^4$, $-Q-Ar$,

and carbon based moieties of up to 24 carbon atoms,
 optionally containing heteroatoms selected from N, S and
 O and optionally substituted by one or more substituents
 independently selected from the groups consisting of -CN,
 -CO₂R, -C(O)NR⁴R⁴, -C(O)-R⁴, -NO₂, -OR⁴, -SR⁴, -NR⁴R⁴,
 -NR⁴C(O)OR⁴, -NR⁴C(O)R⁴ and halogen up to per-halo;
 with each R⁴ independently selected from H or a carbon
 based moiety of up to 24 carbon atoms, optionally
 containing heteroatoms selected from N, S and O and
 optionally substituted by halogen, wherein Q is -O-, -S-,
 -N(R⁴)-, -(CH₂)_β, -C(O)-, -CH(OH)-, -(CH₂)_β-, -(CH₂)_βS-,
 -(CH₂)_βN(R⁴)-, -O(CH₂)_β-CHHal-, -CHal₂-, -S-(CH₂)_β- and
 -N(R⁴)(CH₂)_β- where β = 1-3, and Hal is halogen; and
 Ar is 5- or 6-member aromatic structure containing 0-2
 members selected from the group consisting of nitrogen,
 oxygen and sulfur, which is optionally substituted by
 halogen, up to per-halo, and optionally substituted by Z^{δ1}
 wherein δ1 is 0 to 3 and each Z is independently selected
 from the group consisting -CN, -CO₂R⁴, -C(O)NR⁴R⁴,
 -C(O)-R⁴, -NO₂, -OR⁴, -SR⁴, -SO₂R⁴, -SO₃H, -NR⁴R⁴,
 -NR⁴C(O)OR⁴, -NR⁴C(O)R⁴, and a carbon based moiety of
 up to 24 carbon atoms, optionally containing heteroatoms
 selected from N, S and O and optionally substituted by one
 or more substituents selected from the group consisting of
 -CN, -CO₂R⁴, -C(O)NR⁴R⁴, -C(O)-R⁴, -NO₂, -OR⁴, -SR⁴,
 -SO₂R⁴, -SO₃H, -NR⁴R⁴, -NR⁴C(O)OR⁴, -NR⁴C(O)R⁴, and
 the pharmaceutically acceptable derivatives, salts and
 solvates thereof.

2. Semicarbazide derivative according to claim 1, characterised in that
 each M independently from one another represents a bond or is a

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bridging group, selected from the group consisting of $(CR^4R^4)_h$, or $(CHR^4)_h-Q-(CHR^4)_i$, wherein

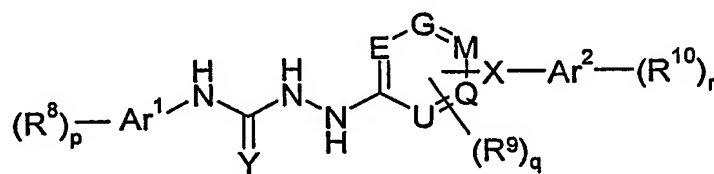
Q is selected from a group consisting of O, S, $N-R^4$, $(CHal_2)_j$, $(O-CHR^4)_j$, $(CHR^4-O)_j$, $CR^4=CR^4$, $(O-CHR^4CHR^4)_j$, $(CHR^4CHR^4-O)_j$, C=O, C=S, C=NR⁴, CH(OR⁴), C(OR⁴)(OR⁴), C(=O)O, OC(=O), OC(=O)O, C(=O)N(R⁴)C(=O), OC(=O)N(R⁴), N(R⁴)C(=O)O, CH=N-NR⁴, OC(O)NR⁴, NR⁴C(O)O, S=O, SO₂, SO₂NR⁴ und NR⁴SO₂, wherein

R⁴ is in each case independently selected from the meanings given above, preferably hydrogen, halogen, alkyl, aryl, aralkyl,

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, preferably 0, 1, 2 or 3, and

j is 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3.

3. Semicarbazide derivative according to claim 1 or 2, selected from the compounds of formula II,



II

wherein

Ar¹, Ar² are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or

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two hetero atoms, independently selected from N, O
und S,

E, G, M, Q and U are selected, independently from one another,
from carbon atoms and nitrogen atoms, with the proviso
that one or more of E, G, M, Q and U are carbon atoms
and that X is bonded to a carbon atom,

R^8 , R^9 and R^{10} are independently selected from a group
consisting of H, A, cycloalkyl comprising 3 to 7 carbon
atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$,
Het, OHet, $N(R^{11})Het$, $(CR^5R^6)_kHet$, $O(CR^5R^6)_kHet$,
 $N(R^{11})(CR^5R^6)_kHet$, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$,
 $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$,
 $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$,
 $NR^{11}(CR^5R^6)_kOR^{13}$, $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,
 $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$,
 $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$,
 $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$,
 $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $CH=N-OA$,
 $CH_2CH=N-OA$, $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$,
 $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$,
 $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{11}$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{11}$,
 $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$,
 $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,
 $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,

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$(\text{CH}_2)_n\text{N}(\text{CH}_2\text{COOR}^{13})\text{COOR}^{14}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{N}(\text{CH}_2\text{CONH}_2)\text{CONH}_2$, $(\text{CH}_2)_n\text{CHR}^{13}\text{COR}^{14}$,
 $(\text{CH}_2)_n\text{CHR}^{13}\text{COOR}^{14}$, $(\text{CH}_2)_n\text{CHR}^{13}\text{CH}_2\text{OR}^{14}$,
 $(\text{CH}_2)_n\text{OCN}$ and $(\text{CH}_2)_n\text{NCO}$, wherein

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R^5, R^6 are in each case independently from one another
 selected from H and A,

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$\text{R}^{11}, \text{R}^{12}$ are independently selected from a group consisting of
 H, A, $(\text{CH}_2)_m\text{Ar}^3$ and $(\text{CH}_2)_m\text{Het}$, or in $\text{NR}^{11}\text{R}^{12}$,

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R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-,
 6- or 7- membered heterocyclus which optionally
 contains 1, 2 or 3 additional hetero atoms, selected from
 N, O and S,

$\text{R}^{13}, \text{R}^{14}$ are independently selected from a group consisting of
 H, Hal, A, $(\text{CH}_2)_m\text{Ar}^4$ and $(\text{CH}_2)_m\text{Het}$,

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A is selected from the group consisting of alkyl, alkenyl,
 cycloalkyl, alkylencycloalkyl, alkoxy, alkoxyalkyl and
 saturated heterocyclyl,

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Ar^3, Ar^4 are independently from one another aromatic hydrocarbon
 residues comprising 5 to 12 and preferably 5 to 10 carbon
 atoms which are optionally substituted by one or more
 substituents, selected from a group consisting of A, Hal,
 NO_2 , CN, OR^{15} , $\text{NR}^{15}\text{R}^{16}$, COOR^{15} , $\text{CONR}^{15}\text{R}^{16}$,
 $\text{NR}^{15}\text{COR}^{16}$, $\text{NR}^{15}\text{CONR}^{15}\text{R}^{16}$, $\text{NR}^{16}\text{SO}_2\text{A}$, COR^{15} ,
 $\text{SO}_2\text{NR}^{15}\text{R}^{16}$, $\text{S(O)}_u\text{A}$ and OOCR^{15} ,

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- Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,
- R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁶, wherein
- Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,
- k, n and m are independently of one another 0, 1, 2, 3, 4, or 5;
- X represents a bond or is (CR¹¹R¹²)_h, or (CHR¹¹)_h-Q-(CHR¹²)_i, wherein
- Q is selected from a group consisting of O, S, N-R¹⁵, (CHal₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, CR¹⁸=CR¹⁹, (O-CHR¹⁸CHR¹⁹)_j, CHR¹⁸CHR¹⁹-O)_j, C=O, C=S, C=NR¹⁵, CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)O, OC(=O), OC(=O)O, C(=)N(R¹⁵), N(R¹⁵)C(=O), OC(=O)N(R¹⁵), N(R¹⁵)C(=O)O, CH=N-O, CH=N-NR¹⁵, OC(O)NR¹⁵, NR¹⁵C(O)O, S=O, SO₂, SO₂NR¹⁵ und NR¹⁵SO₂, wherein
- h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, and
- j is 1, 2, 3, 4, 5 or 6,

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Y is selected from O, S, NR^{21} , $\text{C}(\text{R}^{22})\text{-NO}_2$, $\text{C}(\text{R}^{22})\text{-CN}$ and $\text{C}(\text{CN})_2$, wherein

R^{21} is independently selected from the meanings given for R^{13} , R^{14} , and

R^{22} is independently selected from the meanings given for R^{11} , R^{12} ,

p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

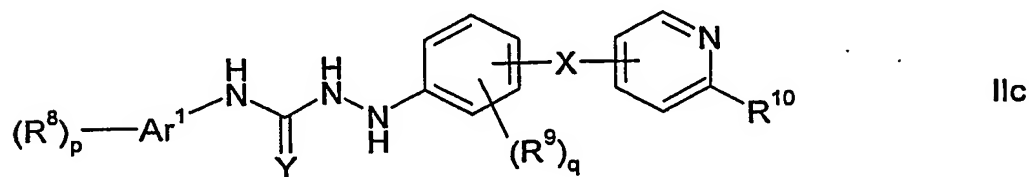
u is 0, 1, 2 or 3, preferably 0, 1 or 2,

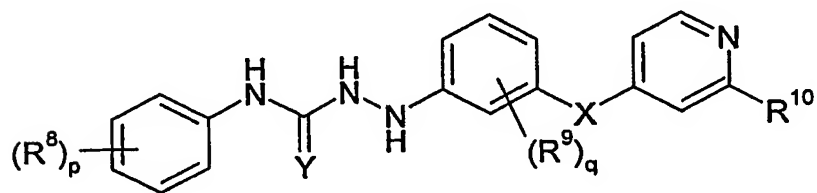
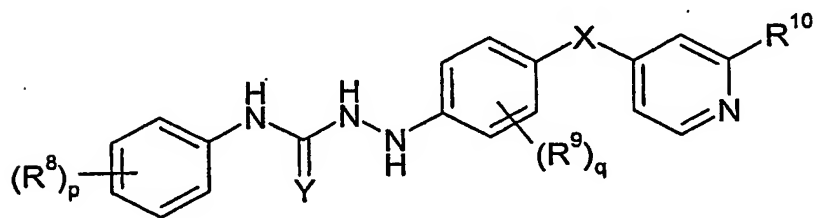
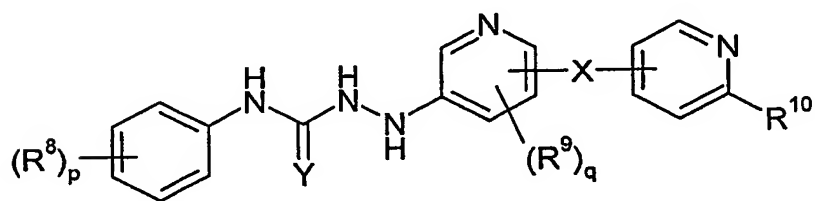
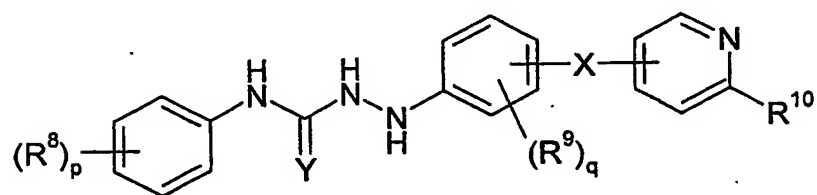
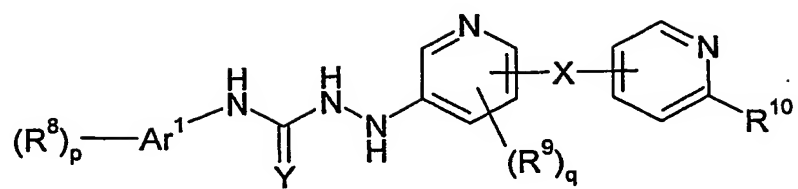
and

Hal is independently selected from a group consisting of F, Cl, Br and I;

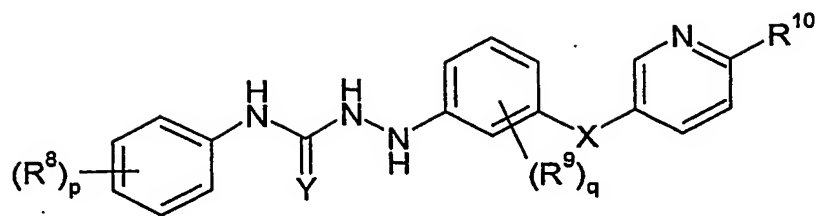
and the pharmaceutically acceptable derivatives, salts and solvates thereof.

4. Semicarbazide derivative according to one of the claims 1 to 3, selected from the compounds of formula IIc, IId, IIe, IIIf, IIg, IIh, IIi, IIj, IIk, IIL, IIm, IIIn, IIo, IIp, IIq, IIr, IIs, IIIt, IIu, IIv, IIw, IIx, IIy and IIz,



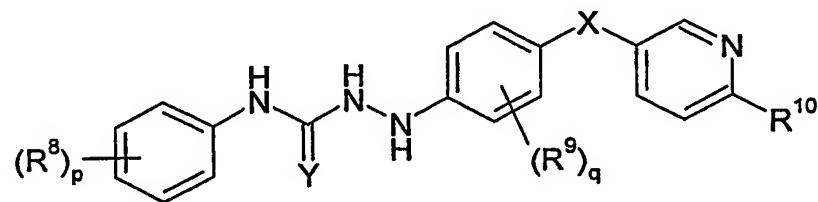


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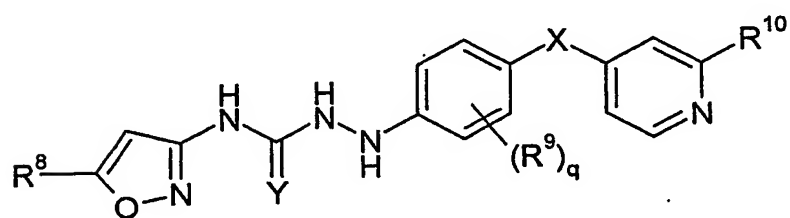
IIIi

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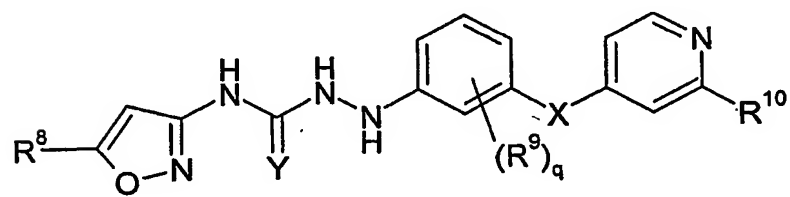
IIj

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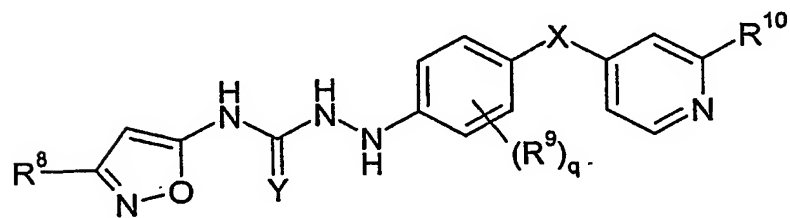
IIIk

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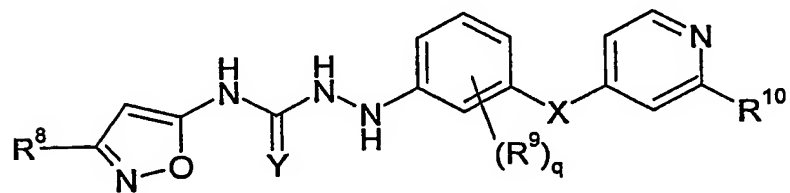
IIl

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IIIm

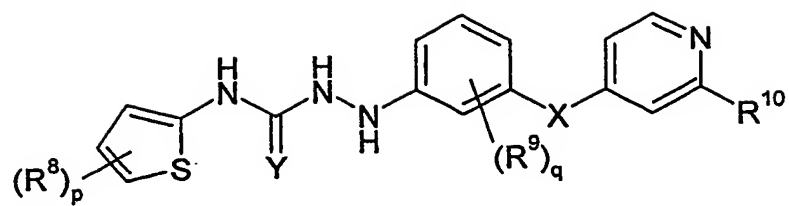
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IIIn

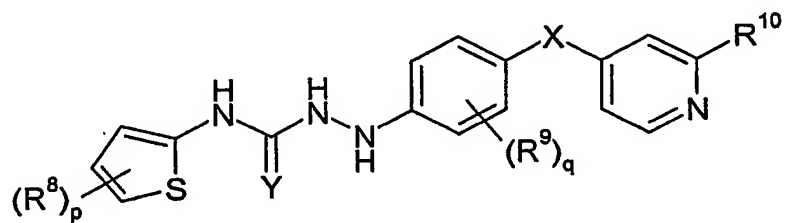
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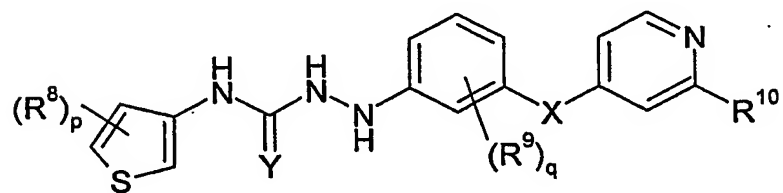
IIo

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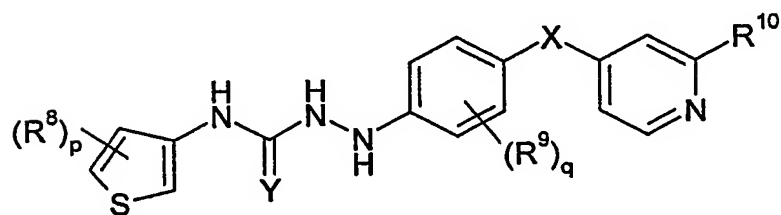
IIp

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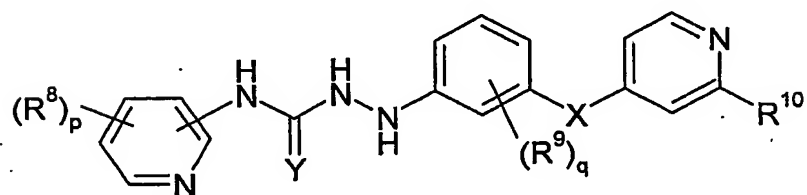
IIq

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IIr

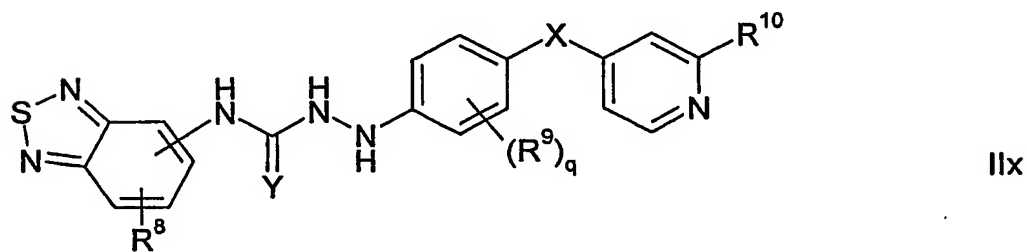
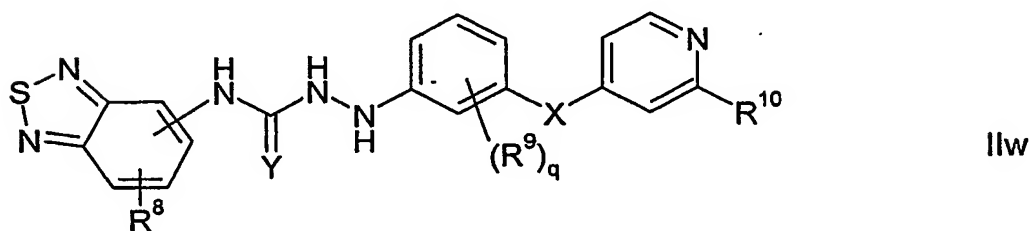
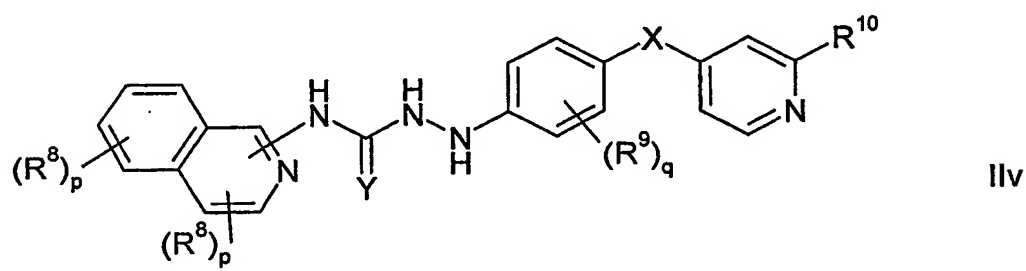
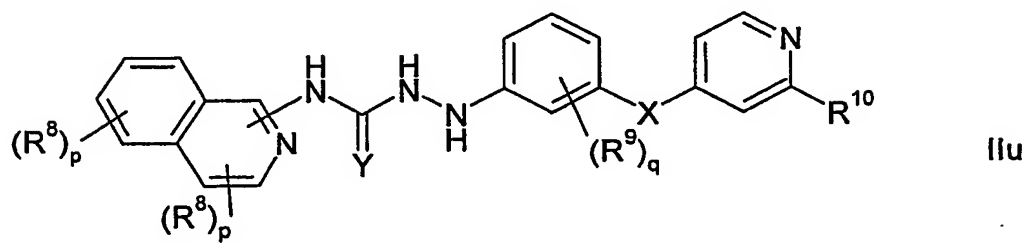
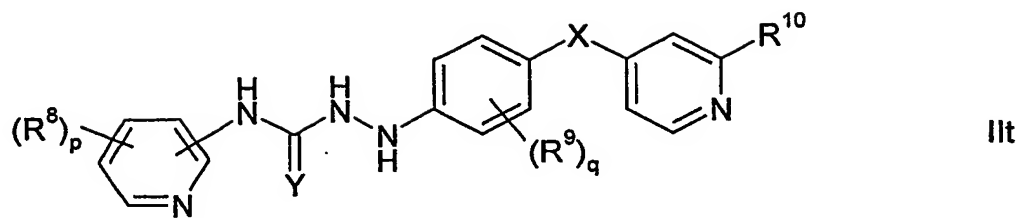
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II s

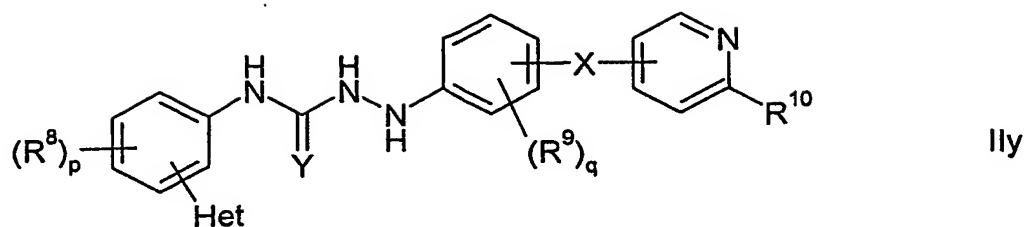
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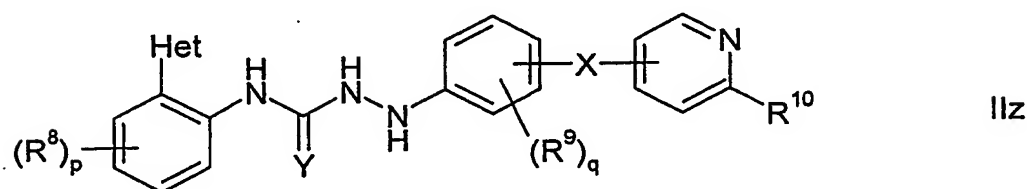


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wherein R^8 , p , Het , Y , X , R^9 and q are as defined in claim 3, R^{10} is H or as defined in claim 3; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

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5. Semicarbazide derivative according to claim one of the claims 1, 2 or 3, selected from the compounds (1) to (224) and/or (225) to (238) of table 1 and/or selected from the compounds 43 to 132 and 138 of table 4, and the pharmaceutically acceptable derivatives, salts and solvates thereof.

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6. Semicarbazide derivative according to one of the claims 1 to 5 as a medicament.
7. Semicarbazide derivative according to one of the claims 1 to 5 as a kinase inhibitor.
8. Semicarbazide derivative according to claim 7, characterized in that the kinases are selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.

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9. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 5.
- 5 10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.
- 10 11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a
15 pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
- 20 12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.
13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.
- 25 14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
- 30 15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by one or more kinases, selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.

16. Use according to claim 13, 14 or 15, characterised in that the disorders are caused, mediated and/or propagated by VEGFR kinases.
- 5 17. Use according to claim 13, 14, 15 or 16, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 10 18. Use according to claim 13, 14, 15, 16 or 17, characterised in that the disorder is cancer.
19. Use according to claim 13, 14, 15, 16 or 17, characterised in that the disorder is noncancerous.
- 15 20. Use according to claim 13, 14, 15, 16, 17 or 19, characterised in that the disorders are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 20 21. Use according to one of the claims 13 to 18, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancer, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
- 25 22. Use according to one of the claims 13 to 19, characterised in that the disorders are selected from the group consisting of arthritis,
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- restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.
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23. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.
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24. Use of a compound according to one of the claims 1 to 5 as a kinase inhibitor.
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25. Use according to claim 24, characterised in that the kinase is one or more kinases selected from the group consisting of raf-kinases, Tie-kinases, PDGFR-kinases, VEGFR-kinases and p38-kinases.
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26. Use of a compound according to one of the claims 1 to 5 as a VEGFR kinase inhibitor.
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27. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.
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28. Method according to claim 27, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are

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administered as a pharmaceutical composition according to claim 9 or 10.

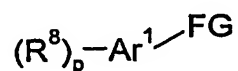
5 29. Method for the treatment and/or prophylaxis of disorders according to claim 27 or 28, characterised in that the disorders are as defined in one of the claims 15 to 23.

10 30. Method for the treatment according to claim 27 or 28, characterised in that the disorder is cancerous cell growth mediated by raf-kinase and/or VEGFR kinase.

31. Method for producing compounds of formula II, characterised in that

a) a compound of formula III

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III

wherein

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FG is a functional group, selected from
 $-N=C=Y$ and $-NH-(C=Y)-LG$,
 wherein Y is as defined as in claim 3 and LG is a leaving
 group,

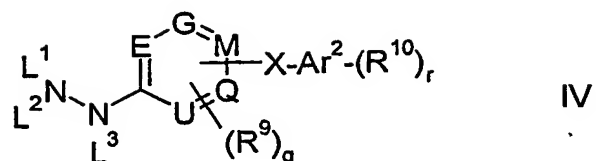
25

is reacted

b) with a compound of IV,

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5 wherein

10 $\text{L}^1, \text{L}^2, \text{L}^3$ are independently from one another H or a metal ion, and
 E, G, M, Q, U, R^9 , q, X, Ar^2 , R^{10} and r are as defined in
 claim 3,

10

 and optionally

 c) isolating and/or treating the compound of formula II obtained by
 said reaction with an acid, to obtain the salt thereof.

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32. Compound of formula III,



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 wherein

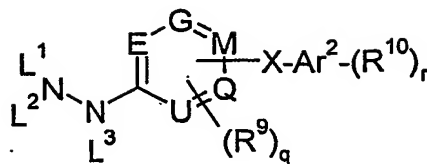
25 FG is a functional group, selected from
 $-\text{N}=\text{C}=\text{Y}$ and $-\text{NH}-(\text{C}=\text{Y})-\text{LG}$,
 wherein Y is as defined as in claim 3 and LG is a leaving
 group.

25

33. Compound of formula IV,

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IV

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wherein

L¹, L², L³ are independently from one another H or a metal ion, and E, G, M, Q, U, R⁹, q, X, Ar², R¹⁰ and r are as defined in claim 3.

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